Evaluation of the effectiveness and costs of inhaled methoxyflurane versus usual analgesia for prehospital injury and trauma

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Supplement 1: Estimation sample and outputs for methoxyflurane against each comparator

Main sample

Table S1.1 Patient numbers and pain scores

	Methoxyflurane	Entonox®	Morphine IV	Paracetamol IV
Patients				
Single dose $n1$	404	-	-	-
Double dose $n21$	7	-	-	-
Double dose $n22$	6	-	-	-
Double dose $n23$	6	-	-	-
Total	423	753	802	278
Patient pain scores				
2 recorded	100%	100%	100%	100%
3 recorded	79.2%	15.4%	32.9%	31.3%
4 recorded	14.9%	1.9%	7.9%	5.8%
5 recorded	4.5%	0.3%	1.4%	1.4%
6 recorded	1.4%	-	-	0.7%
7 recorded	0.2%	-	-	-

Table S1.2 Model parameter estimates

Variable	Methoxyflurane	Entonox®	Methoxyflurane	Morphine IV	Methoxyflurane	Paracetamol IV
Time t	-0.071** (0.004; 0.000)		-0.108** (0.004; 0.000)		-0.081** (0.006; 0.000)	
Time squared t^2	0.001** (0.000; 0.000)		0.001** (0.000; 0.000)		0.001** (0.000; 0.000)	
Treatment d	0.730** (0.251; 0.004)	-	0.422 (0.259; 0.104)	-	0.914** (0.327; 0.005)	-
Treatment x Time dt	-0.135** (0.012; 0.000)	-	-0.088** (0.011; 0.000)	-	-0.128** (0.013; 0.000)	-
Treatment x Time squared dt^2	0.003** (0.000; 0.000)	-	0.002** (0.000; 0.000)	-	0.003** (0.000; 0.000)	-
Sex	-0.402** (0.122; 0.001)	-0.285** (0.088; 0.001)	-0.387** (0.117; 0.001)	-0.048 (0.079; 0.544)	-0.409** (0.124; 0.001)	-0.232 (0.136; 0.087)
Age	-0.003 (0.003; 0.215)	-0.002 (0.002; 0.447)	-0.003 (0.003; 0.226)	-0.001 (0.002; 0.710)	-0.003 (0.003; 0.208)	-0.002 (0.003; 0.584)
Under 18	-0.120 (0.313; 0.701)	-	-0.105 (0.301; 0.727)	-	-0.133 (0.328; 0.685)	-
No GCS	-0.779** (0.216; 0.000)	-	-0.740** (0.206; 0.000)	-	-0.796** (0.225; 0.000)	-
No Trauma	0.284 (0.328; 0.387)	-	0.271 (0.312; 0.385)	-	0.312 (0.333; 0.350)	-
Mild/No Pain	-1.862** (0.450; 0.000)	-	-1.776** (0.428; 0.000)	-	-1.929** (0.460; 0.000)	-
Trauma #2	-0.152 (0.148; 0.305)	0.222 (0.147; 0.131)	-0.143 (0.141; 0.313)	-0.157 (0.108; 0.145)	-0.154 (0.150; 0.305)	-0.228 (0.231; 0.322)
Trauma #3	-0.362* (0.150; 0.016)	0.019 (0.103; 0.852)	-0.344* (0.143; 0.016)	-0.229 (0.123; 0.063)	-0.359* (0.153; 0.019)	-0.136 (0.195; 0.487)
Trauma #4	-0.537** (0.196; 0.006)	-0.038 (0.159; 0.809)	-0.502** (0.187; 0.007)	-0.187 (0.112; 0.096)	-0.528** (0.200; 0.008)	-0.090 (0.182; 0.622)
Trauma #5	-0.048 (0.313; 0.879)	0.062 (0.155; 0.689)	-0.042 (0.299; 0.887)	0.248 (0.146; 0.090)	-0.041 (0.317; 0.898)	-0.211 (0.222; 0.342)
Trauma #6	-0.650 (0.390; 0.096)	-0.048 (0.251; 0.849)	-0.622 (0.372; 0.094)	-0.047 (0.184; 0.800)	-0.658 (0.399; 0.099)	0.181 (0.465; 0.697)
Influence E	-0.046 (0.133; 0.732)	-	-0.019 (0.126; 0.882)	-	-0.051 (0.133; 0.700)	-
Influence P1	0.003 (0.162; 0.987)	-	-0.003 (0.154; 0.986)	-	0.001 (0.165; 0.993)	-
Influence P2	-0.003 (0.236; 0.988)	-	-0.006 (0.227; 0.979)	-	-0.004 (0.242; 0.986)	-

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Influence P3	0.253 (0.254; 0.319)	-	0.237 (0.242; 0.326)	-	0.270 (0.257; 0.293)	-
Compliance	0.707* (0.351; 0.044)	-	0.674* (0.331; 0.042)	-	0.724* (0.349; 0.038)	-
Side-effect	0.064 (0.226; 0.776)	-	0.069 (0.215; 0.748)	-	0.085 (0.230; 0.710)	-
Discontinue	0.399 (0.274; 0.145)	-	0.372 (0.259; 0.151)	-	0.402 (0.273; 0.140)	-
Random effect σ_u^2	0.855** (0.080; 0.000)		0.698** (0.067; 0.000)		0.820** (0.090; 0.000)	
Cut #1 α_1	-3.593** (0.174; 0.000)		-3.713** (0.192; 0.000)		-3.570** (0.285; 0.000)	
Cut #2 α_2	-3.394** (0.168; 0.000)		-3.526** (0.188; 0.000)		-3.308** (0.278; 0.000)	
Cut #3 α_3	-2.921** (0.159; 0.000)		-3.072** (0.183; 0.000)		-2.842** (0.266; 0.000)	
Cut #4 α_4	-2.611** (0.155; 0.000)		-2.750** (0.180; 0.000)		-2.493** (0.260; 0.000)	
Cut #5 α_5	-2.085** (0.150; 0.000)		-2.241** (0.178; 0.000)		-1.977** (0.256; 0.000)	
Cut #6 α_6	-1.418** (0.146; 0.000)		-1.598** (0.173; 0.000)		-1.223** (0.254; 0.000)	
Cut #7 α_7	-0.916** (0.145; 0.000)		-1.145** (0.172; 0.000)		-0.692** (0.253; 0.006)	
Cut #8 α_8	-0.458** (0.145; 0.002)		-0.705** (0.171; 0.000)		-0.234 (0.253; 0.354)	
Cut #9 α_9	0.321* (0.145; 0.027)		0.033 (0.171; 0.845)		0.524* (0.252; 0.038)	
Cut #10 α_{10}	0.759** (0.147; 0.000)		0.440* (0.171; 0.010)		0.890** (0.256; 0.000)	

Notes: $\begin{matrix}\text{estimate}\\(\text{std err; } p\text{-value})\end{matrix}$, $*\ p < 0.05$, $**\ p < 0.01$

Table S1.3 Estimation statistics

Statistic	Methoxyflurane	Entonox®	Methoxyflurane	Morphine IV	Methoxyflurane	Paracetamol IV
Total observations	2907		3211		1934	
Log-pseudolikelihood	-5789.347		-6341.488		-3810.583	
Hypothesis tests						
Clinical efficacy	-11.78 (p<0.001)		-7.98 (p<0.001)		-9.96 (p<0.001)	
All traumas	8.45 (p=0.133)		4.39 (p=0.494)		5.75 (p=0.332)	
Other analgesics	1.07 (p=0.899)		0.97 (p=0.914)		1.21 (p=0.877)	
Serious adverse event	2.50 (p=0.287)		2.48 (p=0.289)		2.68 (p=0.262)	
Time to trough pain	26.41 (0.73; 24.98-27.83)	44.44 (2.50; 39.54-49.34)	26.46 (0.74; 25.02-27.91)	41.76 (1.48; 38.86-44.66)	26.54 (0.75; 25.07-28.00)	40.75 (3.11; 34.65-46.85)

Supplement 2: Estimation sample and outputs for methoxyflurane against each comparator

Per protocol license indication sample

Table S2.1 Patient numbers and pain scores

	Methoxyflurane	Entonox®	Morphine IV	Paracetamol IV
Patients				
Single dose $n1$	387	-	-	-
Double dose $n21$	7	-	-	-
Double dose $n22$	6	-	-	-
Double dose $n23$	6	-	-	-
Total	406	753	802	278
Patient pain scores				
2 recorded	100%	100%	100%	100%
3 recorded	79.6%	15.4%	32.9%	31.3%
4 recorded	14.8%	1.9%	7.9%	5.8%
5 recorded	4.7%	0.3%	1.4%	1.4%
6 recorded	1.5%	-	-	0.7%
7 recorded	0.2%	-	-	-

Table S2.2 Model parameter estimates

Variable	Methoxyflurane	Entonox®	Methoxyflurane	Morphine IV	Methoxyflurane	Paracetamol IV
Time t	-0.071** (0.004; 0.000)		-0.108** (0.004; 0.000)		-0.081** (0.006; 0.000)	
Time squared t^2	0.001** (0.000; 0.000)		0.001** (0.000; 0.000)		0.001** (0.000; 0.000)	
Treatment d	0.742** (0.258; 0.004)	-	0.431 (0.265; 0.104)	-	0.929** (0.333; 0.005)	-
Treatment x Time dt	-0.136** (0.012; 0.000)	-	-0.088** (0.011; 0.000)	-	-0.128** (0.013; 0.000)	-
Treatment x Time squared dt^2	0.003** (0.000; 0.000)	-	0.002** (0.000; 0.000)	-	0.003** (0.000; 0.000)	-
Sex	-0.389** (0.126; 0.002)	-0.285** (0.089; 0.001)	-0.373** (0.120; 0.002)	-0.048 (0.079; 0.542)	-0.396** (0.128; 0.002)	-0.233 (0.136; 0.087)
Age	-0.004 (0.003; 0.211)	-0.002 (0.002; 0.451)	-0.003 (0.003; 0.223)	-0.001 (0.002; 0.710)	-0.004 (0.003; 0.205)	-0.002 (0.003; 0.588)
Trauma #2	-0.149 (0.151; 0.322)	0.223 (0.147; 0.131)	-0.141 (0.144; 0.329)	-0.157 (0.108; 0.146)	-0.152 (0.153; 0.320)	-0.229 (0.232; 0.323)
Trauma #3	-0.369* (0.153; 0.016)	0.019 (0.103; 0.854)	-0.351* (0.146; 0.016)	-0.229 (0.123; 0.063)	-0.366* (0.156; 0.019)	-0.135 (0.196; 0.490)
Trauma #4	-0.540** (0.197; 0.006)	-0.038 (0.160; 0.812)	-0.503** (0.188; 0.007)	-0.187 (0.112; 0.095)	-0.531** (0.202; 0.008)	-0.089 (0.183; 0.625)
Trauma #5	-0.050 (0.317; 0.874)	0.061 (0.156; 0.694)	-0.045 (0.302; 0.883)	0.248 (0.146; 0.090)	-0.043 (0.321; 0.893)	-0.212 (0.223; 0.342)
Trauma #6	-0.656 (0.392; 0.094)	-0.047 (0.252; 0.852)	-0.627 (0.373; 0.092)	-0.047 (0.185; 0.797)	-0.666 (0.401; 0.097)	0.182 (0.467; 0.696)
Influence E	-0.050 (0.138; 0.717)	-	-0.023 (0.131; 0.859)	-	-0.057 (0.139; 0.683)	-
Influence 1	0.023 (0.165; 0.890)	-	0.016 (0.157; 0.918)	-	0.020 (0.169; 0.904)	-
Influence 2	0.006 (0.244; 0.980)	-	0.004 (0.235; 0.987)	-	-0.005 (0.251; 0.983)	-
Influence 3	0.171 (0.271; 0.528)	-	0.157 (0.256; 0.541)	-	0.186 (0.274; 0.496)	-
Compliance	0.693 (0.359; 0.054)	-	0.660 (0.338; 0.051)	-	0.712* (0.357; 0.046)	-
Side-effect	0.059 (0.240; 0.807)	-	0.065 (0.227; 0.774)	-	0.082 (0.243; 0.737)	-
Discontinue	0.427 (0.299; 0.153)	-	0.397 (0.282; 0.160)	-	0.427 (0.298; 0.152)	-

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Random effect σ_u^2	0.876** (0.082; 0.000)	0.712** (0.068; 0.000)	0.849** (0.093; 0.000)
Cut #1 α_1	-3.602** (0.175; 0.000)	-3.718** (0.193; 0.000)	-3.585** (0.287; 0.000)
Cut #2 α_2	-3.397** (0.169; 0.000)	-3.527** (0.188; 0.000)	-3.313** (0.279; 0.000)
Cut #3 α_3	-2.923** (0.160; 0.000)	-3.072** (0.184; 0.000)	-2.846** (0.267; 0.000)
Cut #4 α_4	-2.620** (0.156; 0.000)	-2.756** (0.180; 0.000)	-2.506** (0.261; 0.000)
Cut #5 α_5	-2.090** (0.151; 0.000)	-2.243** (0.178; 0.000)	-1.983** (0.257; 0.000)
Cut #6 α_6	-1.423** (0.147; 0.000)	-1.602** (0.174; 0.000)	-1.227** (0.255; 0.000)
Cut #7 α_7	-0.921** (0.145; 0.000)	-1.149** (0.172; 0.000)	-0.694** (0.254; 0.006)
Cut #8 α_8	-0.458** (0.145; 0.002)	-0.705** (0.171; 0.000)	-0.230 (0.254; 0.364)
Cut #9 α_9	0.317* (0.146; 0.030)	0.028 (0.171; 0.868)	0.520* (0.253; 0.040)
Cut #10 α_{10}	0.763** (0.148; 0.000)	0.441* (0.171; 0.010)	0.896** (0.257; 0.000)

Notes: $\begin{matrix}\text{estimate}\\(\text{std err; } p\text{-value})\end{matrix}$, $*\ p < 0.05$, $**\ p < 0.01$

Table S2.3 Estimation statistics

Statistic	Methoxyflurane	Entonox®	Methoxyflurane	Morphine IV	Methoxyflurane	Paracetamol IV
Total observations	2856		3160		1883	
Log-pseudolikelihood	-5691.349		-6244.257		-3713.417	
Hypothesis tests						
Clinical efficacy	-11.73 (p<0.001)		-7.95 (p<0.001)		-9.93 (p<0.001)	
All traumas	8.42 (p=0.134)		4.43 (p=0.489)		5.80 (p=0.326)	
Other analgesics	0.53 (p=0.971)		0.41 (p=0.982)		0.61 (p=0.961)	
Serious adverse event	2.47 (p=0.291)		2.45 (p=0.295)		2.62 (p=0.270)	
Time to trough pain	26.44 (0.74; 25.00-27.88)	44.46 (2.49; 39.57-49.34)	26.50 (0.75; 25.03-27.97)	41.77 (1.48; 38.87-44.66)	26.57 (0.76; 25.08-28.05)	40.77 (3.11; 34.67-46.87)

Table S2.4 Pathway estimates

Statistic						
Duration severe pain	10.54 (0.70; 9.16-11.91)	Not predicted to exit severe pain state	10.47 (0.69; 9.11-11.83)	20.09 (1.12; 17.88-22.29)	9.66 (0.68; 8.32-11.00)	37.53 (6.58; 24.64-50.42)
Time to trough pain	26.94 (0.74; 25.50-28.38)	44.96 (2.49; 40.07-49.84)	27.00 (0.75; 25.53-28.47)	42.77 (1.48; 39.87-45.66)	27.07 (0.76; 25.58-28.55)	45.77 (3.11; 39.67-51.87)
Pain level at trough	-1.975 (0.177; 0.000)	-0.819 (0.178; 0.000)	-2.162 (0.197; 0.000)	-1.814 (0.189; 0.000)	-1.891 (0.277; 0.000)	-0.762 (0.287; 0.008)
Hypothesis tests						
Equality in times to trough	54.55 (p<0.001)		59.09 (p<0.001)		53.18 (p<0.001)	
Equality in level at trough	25.79 (p<0.001)		6.61 (p=0.010)		20.62 (p<0.001)	

Variables

Denote pain due to trauma by Y^*, where it is an unobservable continuously distributed random variable. Let $S_{ij} = s \in \{0,1,\dots,10\}$ denote the VNPS score reported by patient $i = 1,\dots,N$ taken in sequence $j = 0,1,\dots,T_i$ over time, where S_{i0} denotes the baseline score and T_i is the total number of scores taken on patient i; note that should the score at the time of baseline not be observed then we imputed its value using the last observation carried forward rule. Scores are collected while the patient is under the influence of the target analgesic but not beyond that time, the target analgesic may be either methoxyflurane or one of its comparators. Table S3.1 gives our assumptions on onset and duration for each analgesic.

Table S3.1 Onset and duration of analgesia

Analgesic	Route	Effect begins	Effect ends
Methoxyflurane	inhaled	+30 secs after administration	+5 mins after discontinuation or +45 mins after administration
Entonox®	inhaled	+30 secs after administration	+5 mins after discontinuation or +45 mins after administration
Potency 1	oral	+30 mins after administration	+6 hrs after administration
Potency 2	oral	+30 mins after administration	+6 hrs after administration
Potency 3	oral	+30 mins after administration	+6 hrs after administration
Potency 3	IV	+1 min after administration	+4 hrs after administration
Paracetamol	IV	+5 mins after administration	+6 hrs after administration

Notes:
Intermittent use is assumed for methoxyflurane and Entonox®
Potency 1 (mild): oral paracetamol or ibuprofen
Potency 2 (moderate): oral paracetamol/mild opiate combination
Potency 3 (high): oral opiate or tramadol, parenteral opiate or paracetamol

The relationship between pain and pain score is established by the following set of (ten) observation rules:

$$\Pr(S_{ij} = s|\boldsymbol{X}) = \Pr(\alpha_s < Y_{ij}^* < \alpha_{s+1}|\boldsymbol{X}) \qquad (1)$$

where the conditioning variables $\boldsymbol{X}$ contain all the regressors in the statistical model that is to be specified for Y^*, where we note here that $\boldsymbol{X}$ will include an individual random effect. The cut parameters, collected into vector $\boldsymbol{\alpha} = (\alpha_0, \alpha_1, \dots, \alpha_{11})$, are ordered such that $\alpha_0 < \alpha_1 < \cdots < \alpha_{11}$; as we assume Y^* to be normally distributed then set fixed are $\alpha_0 = -\infty$ and $\alpha_{11} = +\infty$. The point in time (measured in minutes) at which

the j^{th} pain score is taken from the i^{th} patient is denoted $t_{ij} \geq 0$, where baseline $t_{i0} = 0$ is set fixed and corresponds to when the target analgesic was administered. It is important to note that at baseline the effect on pain of the target analgesic has not yet onset (cf Table S3.1).

Model

Under analgesia we expect pain to diminish at a decreasing rate over time. Accordingly, we specified quadratic functions of time to represent the pathways of the response of pain to analgesics. The statistical model was specified with the following structure:

$$Y_{ij}^{*} = (\beta_0 + \theta_0 d_i) + (\beta_1 + \theta_1 d_i) t_{ij} + (\beta_2 + \theta_2 d_i) t_{ij}^2 + d_i \boldsymbol{\gamma}' \boldsymbol{x}_{it} + (1 - d_i) \boldsymbol{\delta}' \boldsymbol{w}_{it} + u_i + \varepsilon_{ij} \quad (2)$$

where the binary dummy d_i is defined such that $d_i = 1$ indicated that methoxyflurane was administered to patient i otherwise when $d_i = 0$ the comparator was the target analgesic. We assumed the individual effect u_i was random (in particular $N(0, \sigma_u^2)$) and independent of all other factors included in the model. Independent regressors were collected into (column) vectors $\boldsymbol{x}$ and $\boldsymbol{w}$, associated parameter coefficients were contained respectively in vectors $\boldsymbol{\gamma}$ and $\boldsymbol{\delta}$ which may vary by target analgesic even if the regressor was common. When regressors were common, we tested for difference of effect using standard single and joint tests. The error term ε_{ij} was assumed independent and identically $N(0, \sigma_\varepsilon^2)$ for all (i, j) pairs. Departures from this ideal were possible so cluster robust standard errors were computed. Two restrictions were required for parameter identification, set were: $\beta_0 = 0$ and $\sigma_\varepsilon^2 = 1$. We used STATA®'s "xtoprobit" routine to estimate the parameters of the model: $(\boldsymbol{\alpha}, \theta_0, \theta_1, \theta_2, \beta_1, \beta_2, \boldsymbol{\gamma}, \boldsymbol{\delta}, \sigma_u^2)$. Estimates were consistent and asymptotically normally distributed under standard statistical assumptions.

Main hypothesis test

Our expectations of response under analgesia over the course of time were consistent with parameter $\beta_1 < 0$. Use of methoxyflurane will attenuate pain faster than its comparator provided the difference parameter $\theta_1 < 0$. We therefore conducted the one-sided hypothesis test (Student t statistic; null distribution approximate $N(0,1)$):

$$H_0: \theta_1 = 0 \text{ versus } H_1: \theta_1 < 0 \quad (3)$$

where rejection of the null hypothesis H_0 provides statistically significant evidence that methoxyflurane relieves pain faster than its comparator.

Finally, additional parameters of interest include the time taken to reach minimum pain or "trough pain". From (2), methoxyflurane's trough pain is predicted to occur at time (in minutes)

$$-\frac{\beta_1+\theta_1}{2(\beta_2+\theta_2)} \quad (4)$$

and for its comparator at time $-\beta_1/2\beta_2$.

Scenario analyses

The following scenario extracts from model (2) a function of time that represents the impact of analgesia on pain over time - the so-called 'pain pathway' - that we compared across treatments. For an assigned value of baseline pain, denoted ω_0, and incorporating into this the duration until onset of analgesia, denoted L_d, pain pathways are given by:

$$P_d(t) = \omega_0 + I\{t \geq L_d\}[(\beta_1 + \theta_1 d)(t - L_d) + (\beta_2 + \theta_2 d)(t - L_d)^2] \quad (5)$$

where indicator $I\{A\} = 1$ if event A is true, otherwise 0. Both pathways, methoxyflurane $P_1(t)$ and comparator $P_0(t)$, had two segments separated according to the length of time in minutes from administration until the onset of analgesia: $L_1 = 0.5$ for methoxyflurane, and comparator L_0 were given in Table S3.1. The duration that an analgesic takes to reduce pain from level ω_0 to a given level $\omega_1 < \omega_0$ is the solution for t to the quadratic equation $P_d(t) = \omega_1$.

We used (5) to estimate the durations a patient spent in severe pain under methoxyflurane and comparator. In particular, we set $\omega_0 = \alpha_{10}$, the level equivalent to the cusp between pain scores of 9 and 10, and $\omega_0 = \alpha_7$, equivalent to the cusp between pain scores of 6 and 7. We then constructed the predicted pathways, $\hat{P}_d(t)$, where all unknown parameters in (5) were replaced with model estimates and solved for durations in $\hat{P}_d(t) = \hat{\alpha}_7$. Graphs of predicted pain pathways $\hat{P}_d(t)$ circumscribed by 95% confidence intervals are provided.